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Interstitial Lung Disease in an Adult With Fanconi Anemia: Clues to the Pathogenesis

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We have studied a 38-year-old man with a prior diagnosis of Holt-Oram syndrome, who presented with diabetes mellitus. He had recently taken prednisone for idiopathic interstitial lung disease and trimethoprim-sulfamethoxazole for sinusitis. Thrombocytopenia progressed to pancytopenia. The patient had skeletal, cardiac, renal, cutaneous, endocrine, hepatic, neurologic, and hematologic manifestations of Fanconi anemia (FA). Chest radiographs showed increased interstitial markings at age 25, dyspnea began in his late 20s, and he stopped smoking at age 32. At age 38, computerized tomography showed bilateral upper lobe fibrosis, lower lobe honeycombing, and bronchiectasis. Pulmonary function tests, compromised at age 29, showed a moderately severe obstructive and restrictive pattern by age 38. Serum alpha-1 antitrypsin level was 224 (normal 85–213) mg/dL and PI phenotype was M1. Karyotype was 46,XY with a marked increase in chromosome aberrations induced in vitro by diepoxybutane.

The early onset and degree of pulmonary disease in this patient cannot be fully explained by environmental or known genetic causes. The International Fanconi Anemia Registry (IFAR) contains no example of a similar pulmonary presentation. Gene-environment (ecogenetic) interactions in FA seem evident in the final phenotype. The pathogenic mechanism of lung involvement in FA may relate to oxidative injury and cytokine anomalies. Am. J. Med. Genet. 69: 315–319, 1997. © 1997 Wiley-Liss, Inc.

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INTRODUCTION

The spectrum of phenotypic variation in Fanconi anemia (MIM: 227650; 227660; 227645; 227646; 600901) continues to broaden. In addition to guiding clinical diagnosis and management, the full delineation of the phenotype can provide insights into molecular pathogenesis. We suggest that interstitial lung disease (ILD) is a syndromic component of FA and review the pulmonary manifestations of FA. Ecogenetic interactions seem evident in FA, and a pathogenic mechanism of lung involvement in FA may be via oxidative injury and cytokine anomalies.

CLINICAL REPORT

A 38-year-old Caucasian man previously diagnosed with Holt-Oram syndrome was admitted for diabetes mellitus (DM) following 1 month of prednisone therapy for chronic ILD. Prior to admission he was treated with trimethoprim-sulfamethoxazole (TMP-SMX) for acute sinusitis. Thrombocytopenia progressed to pancytopenia.

The patient was born to a 35-year-old G7P4A3 woman after a term, uncomplicated pregnancy, with BW 2.6 kg (10th centile). At age 2 months, he was seen for poor weight gain. Measurements were OFC 36 cm (<2nd centile), length 57 cm (3rd centile), weight 3.2 kg (<3rd centile). He lacked both first metacarpals, the right thumb, and had hypoplasia of the left thumb phalanges. Bone age at 6 months was 1 month (<3rd cen-

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tile). Complete blood count (CBC) was normal. Intravenous pyelogram demonstrated two separate calyceal systems on the right and none on the left with crossed fused ectopia; computerized tomography (CT) later confirmed left renal agenesis. A heart murmur was noted in infancy. Cardiac catheterization at 5 years showed a ventriculoseptal defect, which was repaired at 6 years. Right bundle branch block was present. A ventricular (VVIR) pacemaker was placed at age 30 years for 2:1 heart block and revised to a dual-chamber (DDD) pacemaker 3 months before admission because of persistent ventricular pacing. Additional anomalies included inferior vena cava crossover to the left below the hilum of the right kidney, penile hypospadias, an anomalous right third rib, mild thoracic scoliosis, and congenitally small ear canals for which he underwent right tympanostomy and canaloplasty. He finished the ninth grade in special education, was never married, had no offspring, never held a job, could not write, but was able to drive.

The patient was hospitalized for pneumonia at age 10. After a 21-pack-year history of smoking (2 packs per day for 10.5 years), he stopped at age 32. Symptoms of dyspnea began in his late 20s, and chest radiographs showed increased interstitial markings at age 25. By age 38, interstitial markings had increased more in the upper than the lower lobes, with bilateral apical thickening, and lower lobe bullous disease (Fig. 1). Chest CT showed significant bilateral upper lobe fibrosis, lower lobe honeycombing, and traction bronchiectasis (Fig. 2). Pulmonary function tests were consistent with a combined obstructive and restrictive pattern (Table I). Exercise pulse oximetry study showed rapid desaturation to 79% after a short walk. Quantitative alpha-1 antitrypsin (α1AT) level was 224 (normal, 85–213) mg/dL, and PI type was M1. Serum immunoglobulin subclass levels were normal, ruling out immunoglobulin deficiency as a cause of lung disease.

Fig. 1. Chest radiograph, PA view, showing fibrotic changes in upper lung zones with bilateral apical thickening, hyperinflation, and lower lobe bullous disease. A pacemaker is present.

Fig. 2. Computerized tomograph cut through upper lung zone showing mixed fibrotic and emphysematous lung changes with honeycombing.

The patient's father died at age 67 of emphysema and had been a tobacco smoker with symptoms of emphysema in his 40s. His mother had five spontaneous abortions and a full-term male who died at age 3 days. Family history was unremarkable for DM, cardiac, renal, or limb anomalies, and there was no known consanguinity. A 35-year-old sister had a hematologic malignancy, but was reportedly not malformed. She and her mother did not wish further evaluation. The patient was the shortest in the family.

On physical examination, he was 147 cm tall (50th centile for age 11.5 years) and had an OFC of 49.2 cm (<3rd centile; 50th centile for age 2), a frequent dry cough, prepubertal voice, small eyes, hyperpigmented

TABLE I. Pulmonary Function Tests

Pulmonary function test	Age 29 years	Age 38 years
FVC (forced vital capacity): liters, (% predicted)	1.44 (39%)	0.95 (33%)
FEV_1 (forced expired volume in 1 second):liters, (% predicted)	0.74 (23%)	0.37 (16%)
FEV_1/FVC ratio: %	51%	39%
FRC (functional residual capacity): liters, (% predicted)		2.42 (93%)
VC (vital capacity): liters, (% predicted)	1.65 (45%)	0.95 (33%)
DL_{CO} (diffusing capacity of carbon monoxide): ml/min/mmHg, (% predicted)		5.8 (40%)

skin with an aged appearance, petechiae, sparse facial and pubic hair, gynecomastia, a rudimentary left thumb, absent right thumb, limited pronation of the right arm, and bilateral cutaneous syndactyly of the second and third toes. On auscultation of the lungs, scattered inspiratory and expiratory wheezing and dry basilar crackles were heard.

Laboratory Tests

CBC prior to antibiotics and corticosteroids showed an elevated mean corpuscular volume (MCV) of 106.9 (normal, 80.5–99.7) fL but otherwise normal indices. Pancytopenia was documented 6.5 weeks after initiation of TMP-SMX therapy (leukocytes 2.5 (4.5–11.0) × 10^9/L; hemoglobin 11.1 (13.3–17.7) g/dL; hematocrit 31.4 (40.0–52.0) %; MCV 100.8 fL; platelets 31 (150–450) × 10^3/L; reticulocyte count 3.6%; reticulocyte index 1.2%) and resolved spontaneously after antibiotics were stopped. Bone marrow examination demonstrated a hypocellular marrow with trilineage hematopoiesis, dyserythropoiesis, and erythrocyte predominance. Pancytopenia recurred 4 months later after treatment with ampicillin-sulbactam and cefuroxime for acute bronchitis requiring ventilatory support and resolved after withdrawal of antibiotics.

Abnormal liver function tests were interpreted as hepatic dysplasia; peak serum abnormalities were alkaline phosphatase 524 (40–125) IU/L, alanine aminotransferase 67 (<40) IU/L, aspartate aminotransferase 83 (<40) IU/L, gamma-glutamyl transferase 1053 (<65) IU/L. Alpha-fetoprotein was normal. No hepatic lesions were evident on abdominal ultrasonography or computerized tomography. Liver needle biopsy was compatible with dysplastic liver disease and showed mild portal and lobular inflammation with abundant periportal glycogenated nuclei, mild portal fibrosis without evidence of cirrhosis, and mild nuclear pleiomorphism consistent with regeneration. Video esophagram was performed because of the risk of squamous cell carcinoma of the esophagus in FA and demonstrated a small sliding hiatal hernia with marked gastroesophageal reflux but no significant luminal narrowing. Endocrine testing was consistent with hypogonadotrophic hypogonadism with plasma testosterone 2.7 (10.0–42.0) nmol/L, estradiol <10 (0–48) pg/mL, follicle stimulating hormone 7.6 (1.0–12.0) mIU/mL, and luteinizing hormone 4.6 (2.0–12.0) mIU/mL.

MATERIALS AND METHODS

Peripheral blood samples on patient and control received the same day were set up in RPMI 1640 culture medium for chromosomal evaluation and for FA testing. Cultures for karyotyping were incubated for 72 hours, harvested using routine cytogenetic technique, and trypsin Giemsa-banded for analysis. For FA testing, diepoxybutane (DEB) was added after 24 hours to give a final concentration of 0.1 μg/ml to one of two cultures [Auerbach et al., 1981]. Cultures were incubated an additional 48 hours and harvested for metaphases using routine cytogenetic technique. Slides from cultures with and without DEB treatment were solid stained using Giemsa. Chromosome breakage and interchanges were scored in 100 cells per culture.

FAC mutation testing was performed using amplification refractory mutation systems (ARMS) assays as described previously [Verlander et al., 1995].

RESULTS

Studies at the University of Pittsburgh showed the karyotype was 46,XY with spontaneous breaks observed in 5 of 100 cells. The DEB-induced culture contained 20 breaks, 3 quadriradials, 2 interchange configurations, 1 triradial, 1 dicentric, and 1 acentric fragment among 100 cells (normal ⩽10 breaks per 100 cells). Studies repeated at Rockefeller University showed chromosomal breakage frequencies of 0.12 (control range, 0.00–0.05; FA range, 0.02–0.80) and 3.8 (control range, 0.00–0.20; FA range, 1.06–23.9) in baseline and DEB-treated cultures, respectively.

Analysis for *FAC* mutations previously shown to occur in Caucasian patients (IVS4, 322delG, Q13X, R185X, L554P, and R548X) showed that this individual did not carry any of these mutations. Thus this patient is not likely to be in FA complementation group C. Simple screening methods for other FA complementation groups are not available currently.

DISCUSSION

Variable expressivity is characteristic of FA with respect to malformations, age at diagnosis, hematologic involvement, and related illnesses, such as DM, liver dysplasia, and malignancy [Alter, 1993; Auerbach, 1995]. Genetic heterogeneity contributes to the clinical variability, as evidenced by the existence of at least five complementation groups [Strathdee et al., 1992a; Joenje, 1995] and as shown by preliminary genotype-phenotype correlations observed in complementation group C [Verlander et al., 1994]. Phenotypic variability may additionally arise from environmental factors and postzygotic somatic events, perhaps pathogenically related to the in vitro sensitivity to clastogens. A significant contribution of environmental and epigenetic phenomena to the FA phenotype is supported by the observation of discordant phenotypes in monozygotic twin boys [Adler-Brecher et al., 1992], the synchronous onset of pancytopenia in a brother and sister 5 years apart in age [de Vroede et al., 1982], and the lack of concordance of phenotype within sibships [Giampietro et al., 1993]. Thus some patients with FA may go unrecognized, hindering opportunities for medical intervention and genetic counseling.

The mean age of diagnosis of FA in cases reported in the literature is 8.4 years, with a range from birth to 48 years [Alter, 1993]. The late diagnosis of our patient reflects the delay in diagnosis seen in FA patients with congenital anomalies who lack hematologic manifestations [Giampietro et al., 1993], underscoring the importance of increasing the use of DEB testing in patients with congenital malformations to make a timely diagnosis of FA. As illustrated by our patient, the Holt-Oram syndrome typically involves only cardiac and radial ray defects; therefore the diagnosis should be challenged if additional anomalies are present.

An increased incidence of DM in FA is supported by case reports [Farrell 1976; Woodard et al., 1981;

Kennedy et al., 1982; Morrell et al., 1986] and unpublished data from the IFAR. Ecogenetic interactions in FA are illustrated in our patient by the acute onset of DM after corticosteroid therapy and the development of pancytopenia after treatment with marrow-suppressive antibiotics. The latter event is reminiscent of the case of a 4-year-old FA patient with bone marrow aplasia, which improved after discontinuation of cephalexin [Bin-Nun et al., 1993].

FA and ILD

The early onset and severity of obstructive and restrictive pulmonary disease in our patient cannot be fully explained by environmental or known genetic causes. A review of 419 IFAR patients shows 29 patients surviving to 30 years of age or greater; 11 males and 18 females. Pulmonary fibrosis was not reported in any of these patients. Rather, pulmonary alveolar proteinosis is the only reported lung complication [Eldar et al., 1979; Steens et al., 1992]. Although pulmonary alveolar proteinosis and ILD are distinct pathologic conditions, a common thread may be that tumor necrosis factor-alpha (TNFα) is produced by activated macrophages, is induced by mild oxidant stress, and in turn amplifies the production of reactive oxygen species [Pogrebniak et al., 1990]. The combination of FA with ILD [Rubinstein et al., 1995], if true, suggests a pathogenetic relationship to the TNFα overproduction observed in vitro and in vivo as a unique aspect of FA [Rosselli et al., 1994].

The importance of gene-environment interactions in the maintenance of cellular integrity in the lung is well demonstrated in smokers with α1AT deficiency [Ogushi et al., 1991] who develop emphysema prematurely. Tobacco smoke [Chow 1993; Pryor et al., 1993] contains oxidants that can directly inactivate α1AT and recruits phagocytic cells that produce additional oxidants. The activation of alveolar macrophages leads to interleukin-1 and TNFα production, initiating a cascade of inflammation and injury potentially resulting in pulmonary fibrosis [Gauldie et al., 1993]. Transgenic mice with a murine TNFα gene expressed under the control of the human surfactant protein SP-C promoter [Miyazaki et al., 1995] developed severe leukocytic alveolitis, strikingly similar to the pathology observed in human idiopathic pulmonary fibrosis. IL-6 production is deficient in FA cells [Rosselli et al., 1992] and MMC hypersensitivity of FA lymphoblasts was partially corrected by treatment with IL-6 or by anti-TNFα antibodies with a reversal of TNFα overproduction [Rosselli et al., 1994]. Tobacco smoke depresses levels of IL-6 in vitro [Soliman et al., 1992; Dubar et al., 1993; McCrea et al., 1994; Sauty et al., 1994], indicating that cigarette smoking may aggravate the specific cytokine anomalies seen in FA.

Oxidative damage may play a central pathogenetic role in FA [Auerbach et al., 1991; Strathdee et al., 1992b]. Exogenous superoxide dismutase and catalase decrease the frequency of spontaneous chromosome breaks in FA lymphocytes [Nordenson, 1977]; increased oxygen tension correlates positively with spontaneous chromosomal aberrations in FA cells—an effect potentiated by MMC [Joenje et al., 1981, 1983, 1989; Schindler et al., 1988; Hoehne et al., 1989; Saito et al., 1993]; and antioxidants protect against MMC-induced damage [Raj et al., 1980; Dallapiccola et al., 1985; Porfirio et al., 1989; Emerit et al., 1995]. An increase in luminol-dependent chemiluminescence occurs in fresh white blood cells from FA homozygotes [Korkina et al., 1992], indicating excess production of hydroxyl and hydroxyl-like free radicals, predicted to be associated with an increase in 8-hydroxy-2′-deoxyguanosine (8-OHdG). Takeuchi et al. [1993] observed a two- to three-fold increase in 8-OHdG levels from FA homozygotes exposed to hydrogen peroxide. Degan et al. [1995] detected significantly elevated levels of 8-OHdG in fresh blood leukocyte DNA from FA homozygotes, which correlated significantly with chromosome instability and luminol-dependent chemiluminescence. The relevance of oxidative damage in FA to our patient is further supported by the observation of elevated 8-OHdG levels in lung DNA of mice and rats treated with a tobacco-specific nitrosamine [Chung et al., 1992].

Taken together, these studies provide biologic plausibility for ILD as a syndromic component of FA and suggest a possible cellular mechanism for oxidative lung damage in the context of a smoking history. The uniqueness of our patient's presentation may relate to his older age and the cumulative effects of his cigarette use, as most FA patients are young and presumably most do not smoke [Degan et al., 1995]. The clinical course seen here suggests that FA patients should receive an additional exhortation against tobacco use, since they may be especially predisposed to its ill effects.

Diverse assays of oxidative metabolism discussed here in mice with a targeted FA-C gene disruption [Grompe et al., 1995] would be highly interesting. Since the homozygous FA-C mice are phenotypically normal, prenatal exposure to pro-oxidant agents could be performed to try to induce FA-like dysmorphic features and neoplasia, which if successful, would implicate this pathway in the origins of the FA phenotype. A clearer understanding of the pulmonary disease seen in our patient must await further insight into the cellular defects imposed by FA mutations.

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